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COMMENTS ON THE ANALYSIS OF OCCUPATIONAL EXPOSURE TO PCBs AND VARIOUS CANCERS BY THE INDUSTRIAL DISEASE STANDARD PANEL

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The analysis presented in the "Report to the Worker's Compensation Board on Occupational Exposure to PCBs and Various Cancers" is reviewed. It is concluded that important objections can be raised to some of the arguments in the Report. The available evidence does not support the finding of the Report that *"compelling epidemiological evidence of excess cancers appears for the liver, biliary tract and gall bladder cancers."* In fact, the reviewed evidence does not support the existence of a significant link between these cancer incidences and the exposure to PCBs. While such a connection is possible, more information is needed to establish the significance of the link.

1. INTRODUCTION

As requested by Dr. G. Vascotto of the Chemical Research Department, comments are presented on the epidemiological analysis in the "Report to the Workers' Compensations Board on Occupational Exposure to PCBs and various Cancers" prepared by the Industrial Disease Standards Panel (IDSP Report No. 2, December, 1987). According to the Panel, the methodology used in the report is *"a review or 'meta-analysis' ... of all the available data relating to the cancer mortality risk of workers exposed to PCBs during the manufacturing of electrical capacitors"* (page 52). The 'meta-analysis' is an epidemiological analysis, integrating the data of four different studies, none of which is *"sufficiently definite to allow a firm conclusion"*, but when combined *"provide stronger evidence for any relationship between cancer at some site and PCB exposure"* (page 35). The validity of this analysis to draw new conclusions and the Panel's *"compelling epidemiological evidence of excess cancers"* (page 4) are reviewed in this report.

2. REVIEW OF THE EPIDEMIOLOGICAL EVIDENCE

The epidemiological arguments used in the Panel's report are based on a meta-analysis that combines the data of four studies. The combined data were compared with overall combined mortality estimates (the authors explain that such estimates *"would necessarily have to utilize crude estimates of expected deaths for some sites of interest"*). The summary of the results is presented in Table 18 of the report. It indicates a significant increase in the number of deaths due to cancers

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of liver, biliary passages or gall bladder (7 observed vs. 2.54 expected out of 5380 individuals).

In the following, the assumptions and the soundness of the meta-analysis are reviewed.

1. The authors assume that conclusions from the cohort studies can be generalized to the population of all the workers exposed to PCBs. This assumption is unjustifiable.

   In fact, it is observed that the four epidemiological studies concentrate on workers exposed to PCBs during the manufacturing of electrical capacitors. Many of these workers were exposed for extensive periods of time (some of them for over 20 years) and at levels of exposure that were never established. Harbison, et. al. (1987) mention that those levels were very high. Harbison, et. al. (1987) and Carrier (1986) indicate the extent and level of exposure of these workers are not existent in the industry anymore, because PCBs are not currently manufactured and their use is controlled by legislation.

   The above implies that the population of workers used in the study does not represent current populations of workers exposed to PCBs. This is important because it is well known that statistical studies can only be generalized to populations having similar characteristics to the one used in the studies (see Kish, 1987). Therefore, the results of the study can not be generalized to all workers exposed to PCBs.

2. The authors assume that the combined analysis can provide conclusive evidence of the carcinogenic effect of PCBs. This is questionable for the following reasons.

   (i) The combined analysis is an **a posteriori analysis** of the data of the four original studies. The problem with this type of analysis is that it may produce biased results. Therefore, it is useful for obtaining leads for additional work, but inappropriate for drawing new conclusions (Hamilton, 1983, page 443).

   (ii) In the combined analysis no specific hypothesis is formulated prior to the collection of the data, violating a basic assumption for the validity and strength of the conclusions (see Royal, 1986). Hamilton (1983) also notes that "Without a priori hypothesis, false dose-response relationships can be derived" (page 444).

   (iii) The meta-analysis is not a new study that confirms previous findings. Therefore, it can not be used as further evidence to prove the carcinogenicity of PCBs.

   Therefore, the results of the meta-analysis can not be considered *"strong evidence for any relationship between cancer at some site and PCB exposure"* (page 35) as the authors claim.

3. The significant result obtained in Table 18 is questionable. Indeed, when Table 22 is reviewed, the following is observed.

   (i) The two deaths from the Bertazzi study are not confirmed to be primarily due to liver cancer.

   (ii) From the Brown study one death was a metastasis from an unknown primary site and no reports are available for another death (the death due to carcinoma of the biliary system). This last one could have been a metastasis.

   (iii) Only three deaths are confirmed to be due primary to cancer of the liver, biliary tract or gall bladder.

(iv) Two deaths, one death from Bertazzi's and the other from Brown's, have a PCB exposure of only 0.3 years, raising doubts to whether their cancer should be linked to the PCB exposure.

Observe that the error introduced in the estimation of the mortality rates due to the wrong classification of a death is of the same order of magnitude as the estimated value in the study group, whereas it is almost negligible in the population. Therefore, the confirmation of the cancer deaths in the study group is crucial for the analysis.

Because it is not possible to confirm the four cancers mentioned above, one could assign (using the maximum entropy principle) a 50% chance of wrong classification to each of them, and then carry out the statistical test. With this assumption, the number of true cancers can be 3, 4, 5, 6, or 7 with probabilities 0.0625, 0.25, 0.375, 0.25, and 0.0625, respectively. The expected significant level of the test is 0.147. This value is not as compelling as the one presented in Table 18. Therefore, one could conclude that the evidence indicates a possible increase in the incidence of these cancers, but it is difficult to conclude that the increase is significantly larger than the national averages. In fact, the null hypothesis of no increase in cancer deaths due to PCBs exposures (versus the alternative that there is an increase) would not be rejected at the 10% significance level.

4. Table 18 presents 20 statistical associations between PCBs exposure and increase of certain types of cancer deaths. The numbers of significant associations observed in the Table are in close agreement with those expected by chance. In fact, if the probability values of the tests were randomly selected, the likelihood of observing one or more significant results at the 5% level is 64%, and at the 10% level is 88%. Therefore, given the number of statistical associations tested in Table 18, the significant value of liver, biliary passages and gall bladder cancers can not be considered a definite proof of the increase of these cancers due to PCBs exposure.

5. The authors found an association between cancer occurrence and increasing risk categories. The authors use hypothetical relative risks estimated assuming uniform exposure to PCBs during the course of employment. However, from the data in Table 14 the following can be inferred.

   (i) The individuals were exposed to a wide variation of PCB levels.

   (ii) The initial level at which the individuals were exposed could have been much larger than the reported in the Table.

   The above implies that the risks of two individuals working in the same plant, during the same period of time, but at different activities could have been completely different. Furthermore, there could be a tremendous variation in the risk exposure levels of individuals working at different plants. Therefore, the estimated risks could most likely be different from the actual risks obtained using true exposure levels. It is not clear how one could support the conclusion of association between PCBs exposure levels and cancer risks when an assumption used in the calculation of risks may not be valid.

6. Bertazzi et. al. (1987) mention that the workers could have been exposed to trichloroethylene (used in the final step of manufacture) and that a few individuals were also exposed to alkylbenzene and epoxy resins. The meta-analysis does not control for the presence of these chemicals. Holland (1986) indicates that the lack of control for confounding factors (as exposure to other chemicals, or possibly sex, ethnic background, and diet) may invalidate any claim of causation. This is also stated by Hamilton (1983) who observes that, in general, case-control studies are needed to take into account other exposures that might have con-

tributed to any excess of cancers and that until results of case studies are available, no causal relationship between exposure and cancer incidence should be drawn.

7. The authors mention that *"In addition to possibly different exposure conditions in the five facilities under review, the average exposure durations of the individuals in the several cohorts differed substantially"* (page 37). The lack of homogeneity of the populations in the study has also been considered a methodological weakness which may lead to wrong conclusions (see Carrier, 1986).

8. All studies are subject to two types of errors: (i) exposure could be related to cancer but the study reports no significant findings: a false negative association; (ii) exposure may be truly unrelated to cancer but the study reports a significant finding: a false positive association. The authors tried to avoid false negative associations by using the meta-analysis. However, they may be guilty of false positive associations. Ernster (1983) pointed out that *"careful epidemiologists try to guard against the possibility of false positives by carefully controlling for various confounding factors; they should impress upon the public the importance of confirmational studies by other investigations"*. Certainly, this is not the case with the present study.

3. CONCLUSIONS

1. The Panel's statement that *"a probable connection* [exists] *between liver, biliary tract and gall bladder cancers and occupational exposure to PCBs"* is at best incomplete. The statement should also specify (i) the type of exposure that would be linked with cancer and (ii) the strength of such link (see Ernster, 1983). Further studies are required to obtain this information.

2. Even with a more complete statement, several shortcomings in the Panel's analysis can be identified. These include: (i) the fact that a meta-analysis is an a posteriori analysis (not a new study), which may bias the results; (ii) the lack of confirmation of some of the cancers that were used to obtain significant results; (iii) the fact that the significant results could have been expected by chance; (iv) the lack of actual exposure measurements; and (v) the lack of controlling for other confounding factors. These shortcomings question the significance of the results of association, time relationship, and the dose-response relationship between cancer and PCBs exposure and therefore, the conclusions of the report.

3. Harbison et. al. (1987) and Carrier (1986) have also reviewed the evidence of association between PCBs exposure and increase in cancer risk. They have concluded that the evidence is *"inadequate to characterize PCBs as human carcinogens"* (Harbison, 1986, page 29) and that the evidence *"does not allow us to conclude that PCBs have carcinogenic potential in humans"* (Carrier, 1986, page 117). After reviewing the meta-analysis in the Panel's report, it was found that there is not enough evidence to change these conclusions.

4. The perception by the public of the *"probable"* statement may be misdirected, even though the statement could be, in a subjective sense, correct. Indeed, the general public will most likely interpret the finding as a definite association between PCBs exposure and cancer. However, after reviewing the evidence, no strong argument exists to make this conclusion. It would be more precise to say that there is a *possible* connection between liver, biliary tract and gall bladder cancer and occupational exposure to PCBs, although at this time no definite evidence has been found. This would convey the right meaning.

5. What is needed to make a stronger statement is (i) more data, and (ii) data which can be classified according to the measures of relevant external factors (such as the degree of exposure). Such information would assist in reducing the probability of not detecting a significant link between cancer incidence and exposure to PCBs when, in fact, there is such a link. With the information presently available, this probability is not negligible. If this probability is reduced, and still no significant link is detected between the two factors, the stronger statement, that a connection between the types of cancer mentioned and occupational exposure to PCBs is *unlikely*, would be justified.

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